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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Stanley R. Krystek, et al.  
Serial No.: 09/853,918  
Filed: May 10, 2001  
Docket: DB24NP/30436.46USU1  
Title: MODIFIED INOSINE 5'-MONOPHOSPHATE DEHYDROGENASE POLYPEPTIDES AND USES THEREOF

CERTIFICATE UNDER 37 CFR 1.8

I hereby certify that this paper or fee is being deposited with the United States Postal as first class mail in an envelope addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231 on August 2, 2001.

By: Renato Marco P. Domingo  
Name: Renato Marco P. Domingo

Assistant Commissioner for Patents  
Washington, D.C. 20231

Sir:

We are transmitting herewith the attached:

- Transmittal sheet, in duplicate, containing Certificate under 37 CFR 1.8.
- Information Disclosure Statement (37 C.F.R. §1.97(b)(3)) (10 pages)
- Form 1449 (Information Disclosure Statement) (6 sheets)
- Exhibits 1-100 (References)
- Return postcard

Please charge any additional fees or credit overpayment to Deposit Account No. 50-0306. A duplicate of this sheet is enclosed.

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**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

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**Examiner:** Not yet known **TECH CENTER 1600/2900**

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**Group Art Unit:** 1653

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*Renato Marco P. Domingo*

By: Renato Marco P. Domingo

**INFORMATION DISCLOSURE STATEMENT (37 C.F.R. § 1.97(b)(3))**

Assistant Commissioner for Patents  
Washington, D.C. 20231

Dear Sir:

With regard to the above-identified application, the items of information listed on the enclosed Form 1449 are brought to the attention of the Examiner. They are as follows:

- U.S. Patent No. 4,358,535 issued November 9, 1982 – **Exhibit 1**
- U.S. Patent No. 4,603,102 issued July 29, 1986 – **Exhibit 2**
- U.S. Patent No. 4,683,202 issued July 28, 1987 – **Exhibit 3**
- U.S. Patent No. 4,952,394 issued August 28, 1990 – **Exhibit 4**
- U.S. Patent No. 5,110,802 issued May 5, 1992 – **Exhibit 5**
- U.S. Patent No. 5,194,428 issued March 16, 1993 – **Exhibit 6**
- U.S. Patent No. 5,539,082 issued July 23, 1996 – **Exhibit 7**
- U.S. Patent No. 5,585,277 issued December 17, 1996 – **Exhibit 8**
- U.S. Patent No. 5,632,999 issued May 27, 1997 – **Exhibit 9**
- U.S. Patent No. 5,665,583 issued September 9, 1997 – **Exhibit 10**
- U.S. Patent No. 6,128,582 issued October 3, 2000 – **Exhibit 11**

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- International Publication Application No. WO94/24264 published October 27, 1994 – **Exhibit 12**
- International Publication Application No. WO98/24893 published June 11, 1998 – **Exhibit 13**
- Allison, A. C. et al., “Immunological Observations on Patients with Lesch-Nyhan Syndrome, and on the Role of De-Novo Purine Synthesis in Lymphocyte Transformation,” *The Lancet*, vol. II, 1179-82, 1975 – **Exhibit 14**
- Allison, A. C. et al., “The role of de novo purine synthesis in lymphocyte transformation,” *Ciba Foundation Symposium*, 207-24, 1977 – **Exhibit 15**
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- Broglie, Richard et al., “Light-Regulated Expression of a Pea Ribulose-1,5-Bisphosphate Carboxylase Small Subunit Gene in Transformed Plant Cells,” *Science*, 224:838-43, 1984 – **Exhibit 21**
- Caron, Philip C. et al., Engineered Humanized Dimeric Forms of IgG Are More Effective Antibodies,” *The Journal of Experimental Medicine*, 176:1191-5, 1992 – **Exhibit 22**
- Carr, Stephen F. et al., “Characterization of Human Type I and Type II IMP Dehydrogenases,” *J Biol Chem*, 268:27286-90, 1993 – **Exhibit 23**

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- Carter, Paul et al., "Humanization of an anti-p185<sup>HER2</sup> antibody for human cancer therapy," *Proc Natl Acad Sci USA*, 89:4285-9, 1992 – **Exhibit 24**
- Cohen, Stanley N. et al., "Nonchromosomal Antibiotic Resistance in Bacteria: Genetic Transformation of *Escherichia coli* by R-Factor DNA," *Proc Natl Acad Sci USA*, 69:2110-4, 1972 – **Exhibit 25**
- Colbère-Garapin, Florence et al., "A New Dominant Hybrid Selective Marker for Higher Eukaryotic Cells," *J Mol Bio*, 150:1-14, 1981 – **Exhibit 26**
- Colby, Thomas D. et al., "Crystal structure of human type II inosine monophosphate dehydrogenase: Implications for ligand binding and drug design," *Proc Natl Acad Sci USA*, 96:3531-6, 1999 – **Exhibit 27**
- Collart, Frank R. and Eliezer Huberman, "Amplification of the IMP Dehydrogenase Gene in Chinese Hamster Cells Resistant to Mycophenolic Acid," *Mol Cell Biol*, 7:3328-31, 1987 – **Exhibit 28**
- Collart, Frank R. and Eliezer Huberman, "Cloning and Sequence Analysis of the Human and Chinese Hamster Inosine-5'-monophosphate Dehydrogenase cDNAs," *J Biol Chem*, 263:15769-72, 1988 – **Exhibit 29**
- Collart, F. R. et al., "Increased Inosine-5'-phosphate Dehydrogenase Gene Expression in Solid Tumor Tissues and Tumor Cell Lines," *Cancer Res*, 52:5826-8, 1992 – **Exhibit 30**
- Cooney, David A. et al., "The Conversion of 2-β-D-Ribofuranosylthiazole-4-carboxamide to an Analogue of NAD with Potent IMP Dehydrogenase-Inhibitory Properties," *Biochem Pharm*, 31:2133-6, 1982 – **Exhibit 31**
- Coruzzi, Gloria et al., "Tissue-specific and light-regulated expression of a pea nuclear gene encoding the small subunit of ribulose-1,5-bisphosphate carboxylase," *EMBO J*, 3:1671-9, 1984 – **Exhibit 32**
- Crabtree, G. W. and J. Frank Henderson, "Rate-limiting Steps in the Interconversion of Purine Ribonucleotides in Ehrlich Ascites Tumor Cells *in Vitro*," *Cancer Res*, 31:985-91, 1971 – **Exhibit 33**

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- Dugas, Hermann and Christopher Penney, *Bioorganic Chemistry*, Springer-Verlag, NY, 54-92 – **Exhibit 36**
- Engelhard, E. K. et al., "The insect tracheal system: A conduit for the systemic spread of *Autographa californica* M nuclear polyhedrosis virus," *Proc Natl Acad Sci USA*, 91:3224-7, 1994 – **Exhibit 37**
- Fell, H. Perry et al., "Homologous recombination in hybridoma cells: Heavy chain chimeric antibody produced by gene targeting," *Proc Natl Acad Sci USA*, 86:8507-11, 1989 – **Exhibit 38**
- Fields, Stanley and Ok-kyu Song, "A novel genetic system to detect protein-protein interactions," *Nature*, 340:245-6, 1989 – **Exhibit 39**
- Fleming, Mark A. et al., "Inhibition of IMPDH by Mycophenolic Acid: Dissection of Forward and Reverse Pathways Using Capillary Electrophoresis," *Biochemistry*, 35:6990-7, 1996 – **Exhibit 40**
- Franklin, T. J. and Jennifer M. Cook, "The Inhibition of Nucleic Acid Synthesis by Mycophenolic Acid," *Biochem J*, 113:515-24, 1969 – **Exhibit 41**
- Gilbert, Harry J. et al., "Inosine-5'-Monophosphate Dehydrogenase of *Escherichia coli*," *Biochem J*, 183:481-94, 1979 – **Exhibit 42**
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- Hager, Paul W. et al., "Recombinant Human Inosine Monophosphate Dehydrogenase Type I and Type II Proteins," *Biochem Pharmacol*, 49:1323-9, 1995 – **Exhibit 47**
- Hannon, Gregory J. et al., "Isolation of the Rb-related p130 through its interaction with CDK2 and cyclins," *Genes and Development*, 7:2378-91, 1993 – **Exhibit 48**
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- Neuberger, Michael S. et al., "Recombinant antibodies possessing novel effector functions," *Nature*, 312:604-8, 1984 – **Exhibit 70**
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- Shaw, Leslie M. et al., "Mycophenolate Mofetil: A Report of the Consensus Panel," *Therapeutic Drug Monitoring*, 17:690-99, 1995 – **Exhibit 77**
- Shope, Bob, "A Genetically Engineered Human IgG Mutant with Enhanced Cytolytic Activity," *J Immunol*, 148:2918-22, 1992 – **Exhibit 78**

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- Sims, Martin J. et al., "A Humanized CD18 Antibody Can Block Function without Cell Destruction," *J Immunol*, 151:2296-308, 1993 – **Exhibit 79**
- Sintchak, Michael D. et al., "Structure and Mechanism of Inosine Monophosphate Dehydrogenase in Complex with the Immunosuppressant Mycophenolic Acid," *Cell*, 85:921-30, 1996 – **Exhibit 80**
- Smith, Camilla M. et al., "Inhibitors of Inosinate Dehydrogenase Activity in Ehrlich Ascites Tumor Cells *in Vitro*," *Biochem Pharmacol*, 23:2727-35, 1974 – **Exhibit 81**
- Smith, Gale E. et al., "Molecular Engineering of the *Autographa californica* Nuclear Polyhedrosis Virus Genome: Deletion Mutations Within the Polyhedrin Gene," *J Virol*, 46:584-93, 1983 – **Exhibit 82**
- Snyder, Floyd F. et al., "Inhibition of Purine Metabolism – Computer-Assisted Analysis of Drug Effects," *Biochem Pharmacol*, 21:2351-7, 1972 – **Exhibit 83**
- Southern, E. M., "Detection of Specific Sequences Among DNA Fragments Separated by Gel Electrophoresis," *J Mol Biol*, 98:503-17, 1975 – **Exhibit 84**
- Takamatsu, Nobuhiko et al., "Expression of bacterial chloramphenicol acetyltransferase gene in tobacco plants mediated by TMV-RNA," *EMBO Jour*, 6:307-11, 1987 – **Exhibit 85**
- Tan, Lee K. et al., "A Human-Mouse Chimeric Immunoglobulin Gene with a Human Variable Region is Expressed in Mouse Myeloma Cells," *J Immunol*, 135:3564-7, 1985 – **Exhibit 86**
- Thorpe, Philip E. and Walter C. J. Ross, "The Preparation and Cytotoxic Properties of Antibody-Toxin Conjugates," *Immuno Rev*, 62:119-58, 1982 – **Exhibit 87**
- Van Heeke, Gino and Sheldon M. Schuster, "Expression of Human Asparagine Synthetase in *Escherichia coli*," *J Biol Chem*, 264:5503-9, 1989 – **Exhibit 88**
- Vaughan, Tristan J. et al., "Human Antibodies by Design," *Nature Biotechnology*, 16:535-9, 1998 – **Exhibit 89**
- Verhoeyen, Martine et al., "Reshaping Human Antibodies: Grafting and Antilysozyme Activity," *Science*, 239:1534-6, 1988 – **Exhibit 90**

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- Wigler, Michael et al., "DNA-mediated transfer of the adenine phosphoribosyltransferase locus into mammalian cells," *Proc Natl Acad Sci USA*, 76:1373-6, 1979 – **Exhibit 91**
- Wigler, Michael et al., "Transfer of Purified Herpes Virus Thymidine Kinase Gene to Cultured Mouse Cells," *Cell*, 11:223-32, 1977 – **Exhibit 92**
- Wigler, M. et al., "Transformation of mammalian cells with an amplifiable dominant-acting gene," *Proc Natl Acad Sci USA*, 77:3567-70, 1980 – **Exhibit 93**
- Wiseman, Thomas et al., "Rapid Measurement of Binding Constants and Heats of Binding Using a New Titration Calorimeter," *Anal Biochem*, 179:131-7, 1989 – **Exhibit 94**
- Wolff, Edith A. et al., "Monoclonal Antibody Homodimers: Enhanced Antitumor Activity in Nude Mice," *Cancer Res*, 53:2560-5, 1993 – **Exhibit 95**
- Xiang, Bosong et al., "Monovalent Cation Activation and Kinetic Mechanism of Inosine 5'-Monophosphate Dehydrogenase," *J Biol Chem*, 271:1435-40, 1996 – **Exhibit 96**
- Yang, Meijia et al., "Protein-peptide interactions analyzed with the yeast two-hybrid system," *Nucleic Acids Res*, 23:1152-6, 1995 – **Exhibit 97**
- Zamecnik, Paul C. and Mary L. Stephenson, "Inhibition of Rous sarcoma virus replication and cell transformation by a specific oligodeoxynucleotide," *Proc Natl Acad Sci USA*, 75:280-4, 1978 – **Exhibit 98**
- Zamecnik, Paul C. et al, "Inhibition of replication and expression of human T-cell lymphotropic virus type III in cultured cells by exogenous synthetic oligonucleotides complementary to viral RNA," *Proc Natl Acad Sci USA*, 83:4143-6, 1986 – **Exhibit 99**
- Zimmerman, Albert G. et al., "Characterization of the Human Inosine-5'-monophosphate Dehydrogenase Type II Gene," *J Biol Chem*, 270:6808-14, 1995 – **Exhibit 100**

This statement should be considered because it is submitted before the mailing date of the first Office Action on the merits according to 37 C.F.R. §1.97(b)(3). In accordance with 37 C.F.R. §1.98(a)(2), copies of each document or other information listed on the enclosed Form 1449 are provided.

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No representation is made that a reference is "prior art" within the meaning of 35 U.S.C. §§ 102 and 103 and Applicants reserve the right, pursuant to 37 C.F.R. § 1.131 or otherwise, to establish that the reference(s) are not "prior art." Moreover, Applicants do not represent that the references have been thoroughly reviewed or that any relevance of any portion of a reference is intended.

Consideration of the items listed is respectfully requested. Pursuant to the provisions of M.P.E.P. § 609, it is requested that the Examiner return a copy of the attached Form 1449, marked as being considered and initialed by the Examiner, to the undersigned with the next official communication.

No fee is deemed necessary in connection with the filing of this Information Disclosure Statement. However, if any additional fee is required, authorization is hereby given to charge the amount of any such fee, or credit any overpayment, to Deposit Account No. 50-0306.

Respectfully submitted,

Sarah B. Adriano

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FORM 1449*		Docket Number DB24NP/30436.46USU1	Application Number 09/853,918
INFORMATION DISCLOSURE STATEMENT IN AN APPLICATION		Applicant Stanley R. Krystek et al.	
(Use several sheets if necessary)		Filing Date May 10, 2001	Group Art Unit 1653

## U.S. PATENT DOCUMENTS

EXAMINER INITIAL	DOCUMENT NO.	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE
✓	4,358,535 (Exhibit 1)	11/09/82	Falkow et al.			12/08/80
✓	4,603,102 (Exhibit 2)	07/29/86	Himmelmann et al.			06/26/85
✓	4,683,202 (Exhibit 3)	07/28/87	Kary B. Mullis			10/25/85
✓	4,952,394 (Exhibit 4)	08/28/90	Peter D. Senter			11/23/87
✓	5,110,802 (Exhibit 5)	05/05/92	Cantin et al.			07/14/87
✓	5,194,428 (Exhibit 6)	03/16/93	Agrawal et al.			04/30/90
✓	5,539,082 (Exhibit 7)	07/23/96	Nielsen et al.			04/26/93
✓	5,585,277 (Exhibit 8)	12/17/96	Bowie et al.			03/21/95
✓	5,632,999 (Exhibit 9)	05/27/97	Thomas A. Miller			08/18/93
✓	5,665,583 (Exhibit 10)	09/09/97	Collart et al.			08/12/88
✓	6,128,582 (Exhibit 11)	10/03/00	Wilson et al.			04/30/96

## FOREIGN PATENT DOCUMENTS

	DOCUMENT NO.	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION	
						YES	NO
✓	WO94/24264 (Exhibit 12)	10/27/94	PCT				X
✓	WO98/24893 (Exhibit 13)	06/11/98	PCT				X

## OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)

✓	Allison, A. C. et al., "Immunological Observations on Patients with Lesch-Nyhan Syndrome, and on the Role of De-Novo Purine Synthesis in Lymphocyte Transformation," <i>The Lancet</i> , vol. II, 1179-82, 1975 (Exhibit 14)
✓	Allison, A. C. et al., "The role of de novo purine synthesis in lymphocyte transformation," <i>Ciba Foundation Symposium</i> , 207-24, 1977 (Exhibit 15)
✓	Arnon, Ruth et al., "Monoclonal Antibodies for Immunotargeting of Drugs in Cancer Therapy," <i>Monoclonal Antibodies and Cancer Therapy</i> , Reisfeld and Sell (eds.), 243-256 (Alan R. Liss, Inc., NY), 1985 (Exhibit 16)
✓	Berent, Susan L. et al., "Comparison of Oligonucleotide and Long DNA Fragments as Probes in DNA and RNA Dot, Southern, Northern, Colony and Plaque Hybridizations," <i>Biotechniques</i> , 3:208-18, 1985 (Exhibit 17)

EXAMINER	DATE CONSIDERED
EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; draw line through citation if not in conformance and not considered. Include copy of this form for next communication to the Applicant.	

FORM 1449*		Docket Number DB24NP/30436.46USU1	Application Number 09/853,918
INFORMATION DISCLOSURE STATEMENT IN AN APPLICATION		Applicant Stanley R. Krystek et al.	
(Use several sheets if necessary)		Filing Date May 10, 2001	Group Art Unit 1653

OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)			
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